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ARCHIVES OF PEDIATRICS

A MONTHLY DEVOTED TO THE

DISEASES OF INFANTS AND CHILDREN

JOHN FITCH LANDON, M.D., Editor

LEADING ARTICLES IN THIS NUMBER

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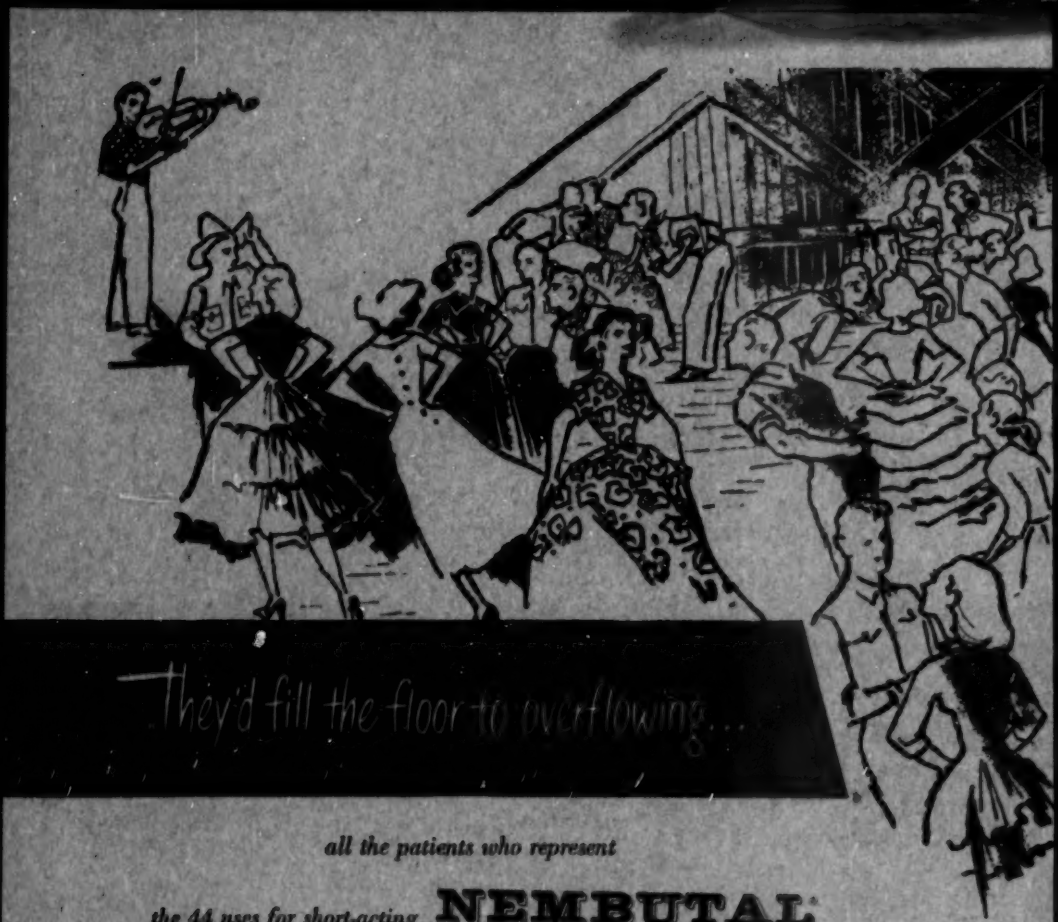

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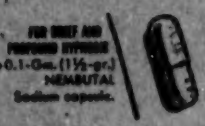

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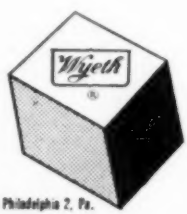

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1. Grayzel, H. G., Helmer, C. B., and Grayzel, R. W.: New York St. J. M. 53:2233, 1953.
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ARCHIVES OF PEDIATRICS

VOL. 70 NOVEMBER 1953 No. 11

JOHN FITCH LANDON, M.D., Editor

SPINAL FLUID THERAPY IN PURULENT MENINGITIS

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Introduction. The principle in treating purulent infections is to increase the defensive mechanisms of the body or intensify the antibacterial power through the use of antibiotics or other chemotherapeutics. The discovery of prontosil by Domagk in 1935 and the subsequent progress of the sulfonamids, the development of penicillin in 1941 by Abraham, the discovery of streptomycin in 1944 by Wacksman and the rapid introduction of other antibiotics have brought unmeasurable hope to mankind in the treatment of purulent infections and there have been many reports on the effectiveness of these agents in the treatment of purulent meningitis. However, on the other hand, the toxicity, untoward reactions, appearance of resistant strains and other defects of these agents (Welch 1943, Schmidt 1944, van Dyke 1945, Forey 1945) have become a great problem for the clinician. Furthermore, the reports of O'Meara, McNally and Nelson, in 1947, on the mechanism of action of sulfonamids and that of Flory on the action of antibiotics has shown that the effect of these agents is bacteriostatic and that the actual removal of the infectious agent is up to the defensive action of the body, especially the phagocytic action of the leucocytes and the activity of the immune bodies, and it has become clear that the chemical agents have little effect on the development of these immunological mechanisms. It is felt that the treatment of purulent meningitis has entered a stage of reconsideration. To support this

is the fact that sulfonamids or antibiotics are no longer used singly in the treatment of purulent meningitis; it has been found that drugs possessing different mechanisms of action or differing therapeutic actions used together are more effective. The use of small amounts of differing drugs not only prevents the occurrence of resistance and intensifies the antibacterial action through their cumulative action but the toxicity and side effects of each drug is reduced. Another method is to intensify the defensive action of the host which has been weakened by the infection and accelerate the production of immune bodies through the use of chemical agents and immunological therapy or blood transfusions and in this way lead to natural recovery. In this sense I would like to introduce the method of simultaneously using antibiotics and cerebrospinal fluid for the treatment of purulent meningitis.

Reports of the use of cerebrospinal fluid in treatment are few. Egami of Tohoku University reported, in 1926, of the bacteriocidic action of spinal fluid of humans and rabbits toward the typhoid bacillus. Paul and Sara reinvestigated this work, but their results do not agree with Egami. In 1934 Toräk reported that therapeutic results were improved when the spinal fluid is drawn and then reinjected into the same patient intraspinally in the early stage of poliomyelitis. Besides these, there are one or two other reports in the field of otolaryngolgy but no complete study has been reported as yet.

Method. The method is extremely simple. After removing a quantity of spinal fluid from the patient, 10-20 cc. of spinal fluid, drawn from the parents or other children, is slowly injected intrathecally. As a rule injections are carried out once a day but this must be continued every single day. When antibiotics are used, the antibiotic is injected in the morning and the spinal fluid injected in the afternoon. Antibiotics are used only during the acute stage and spinal fluid alone is continued until the findings in the spinal fluid become negative.

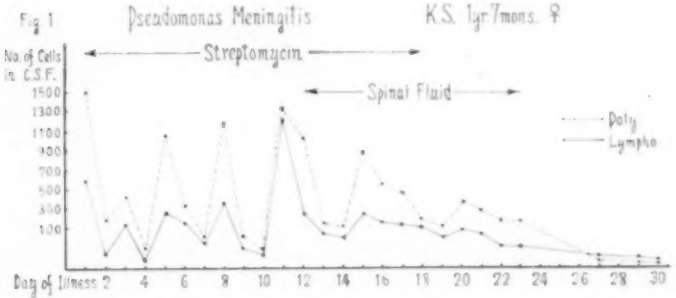
CASE REPORTS

1. PSEUDOMONAS MENINGITIS. In the summer of 1949, 10 cases of meningitis due to Pseudomonas were admitted to the pediatric department of the Osaka University Hospital. Six cases recovered promptly with intrathecal streptomycin, but there were frequent relapses in the remaining four and streptomycin had to

be discontinued due to side reactions as rash, vomiting and in severe cases convulsions. Spinal fluid (15 cc.) was drawn from the patients who had recovered and injected once daily in these four patients after removing 25 cc. of spinal fluid. This was surprisingly effective and there was a great improvement in the general condition of the patients and the findings in the spinal fluid improved. An uneventful and rapid recovery was made.

Case 1. K. K., 7 years 4 month old boy.

As can be seen in the chart (Fig. 1) the course was stormy with frequent relapses and further response to streptomycin could not be seen. On the 18th day, a rash broke out so streptomycin was discontinued and spinal fluid alone was injected every day. The meningeal signs disappeared and the findings in the spinal fluid improved and there was complete recovery by the 30th day of illness.

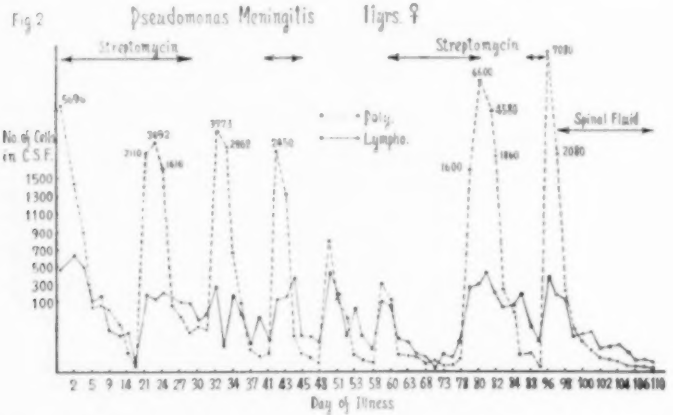


Case 2. K. U., 11 year old girl.

Treatment with streptomycin had to be discontinued from time to time due to occurrence of rash, vomiting, convulsions and other side effects and as a result there was frequent relapse. A prompt improvement was observed upon instillation of the spinal fluid therapy. This is one of the cases in which this type of treatment was most effective (Fig. 2).

The Agglutinin Content of the Cerebrospinal Fluid. The opinion of investigators differs in regards to the presence of agglutinin in the cerebrospinal fluid. It cannot be found in passive immunity, and in active immunity a trace can be seen only when

the agglutinin content of the blood is over 5,000. It is found in measurable quantity in the spinal fluid only when bacteria can be demonstrated. It would be most simple to explain the effect of spinal fluid if large quantities of immune bodies were present in the spinal fluid, since the spinal fluid used was taken from patients in the reconvalescent period. With this aim, the spinal fluid of six patients in the reconvalescent period, 30 days after contraction of illness, was examined for agglutinin content. It was positive with the 1:8 dilution in one case and with the 1:2 dilution in another but could not be demonstrated in the remaining four cases. On the 40th day all six were negative with the 1:2 dilution.

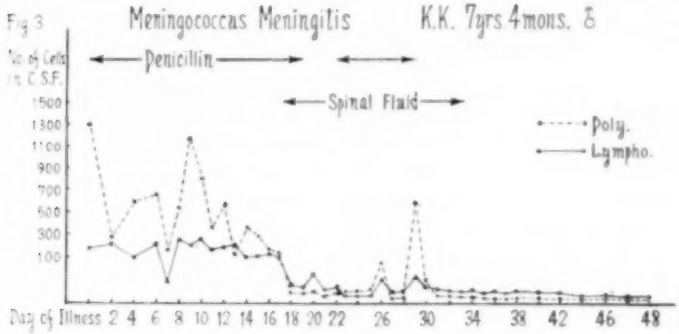


From this fact it is difficult to explain the action of convalescent spinal fluid through the presence of immune bodies. It was therefore thought that the same effect could be obtained by the injection of normal spinal fluid, so normal spinal fluid was tried in the treatment of purulent meningitis.

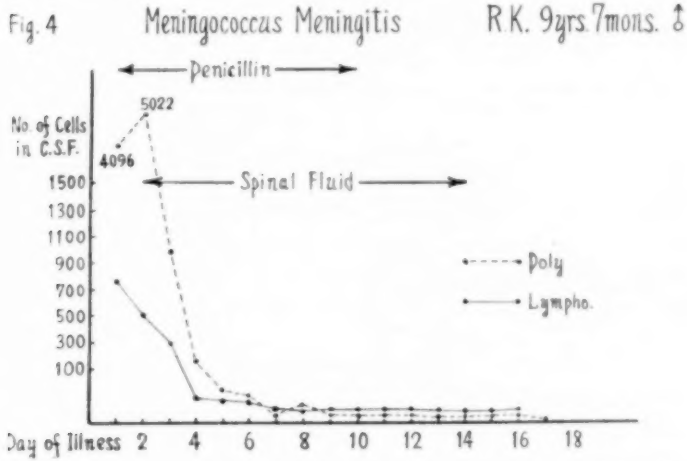
II. MENIGOCOCCUS MENINGITIS. Many cases of meningococcus meningitis are encountered where prognosis is poor due to decline in general condition resulting from frequent relapses arising from the attaining of resistance of the bacteria towards penicillin. In such cases it is possible to accelerate recovery by treatment with cred a reaction to penicillin. Penicillin was stopped and spinal fluid improve within a short time.

Case 1. K. K., 7 years 4 month old boy.

Penicillin therapy was started upon hospitalization but even after 16 days there were frequent relapses and meningeal signs did not



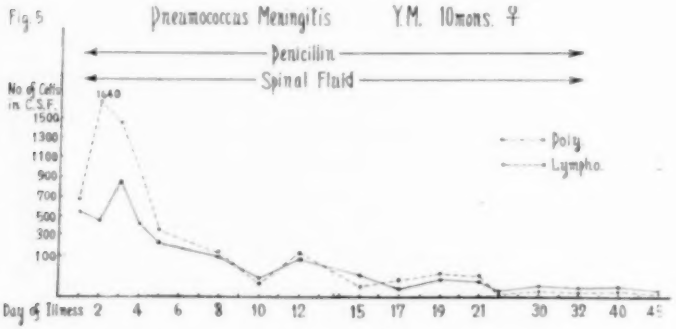
clear up and there was no decrease in the number of cells in the spinal fluid. Spinal fluid therapy was started on the 17th day and there was immediate improvement in the findings; by the sixth injection the cells in the spinal fluid had decreased to less than 50



and the meningeal signs had all but disappeared. On the 29th day there was a temporary increase in cells to 700, but the general con-

dition was good and meningeal signs were absent so it was considered to be a reaction to penicillin. Penicillin was stopped and spinal fluid alone continued; the following day, there was a prompt decrease in cells and recovery was uneventful (Fig. 3).

Fig. 5



Case 2. R. K., 9 years 7 month old boy.

At time of admittance vomiting and convulsions were severe and sensorium was disturbed. The spinal fluid was pus-like and the cells were too numerous for counting. After two injections of spinal fluid, the number of cells dropped to less than 200 and the

Fig. 6

	No. of Cases	Cases Cured	Percentage Recovery
Meningococcus Meningitis	10	10	100 %
Pneumococcus Meningitis	10	8	80 %
Influenza Meningitis	9	6	66.6%

sensorium became clear. The meningeal signs disappeared on the 6th day (Fig. 4).

III. PNEUMOCOCCUS MENINGITIS.

Case 1. T. F., 5-year-old girl.

At time of hospitalization the sensorium was clouded and there were strong meningeal signs present. The cerebrospinal fluid was clouded and the cell count was 2,600. Penicillin and spinal fluid therapy were started and, after the 3rd treatment, the number of cells decreased to less than 100, and sensorium become clear with improvement in the meningeal signs. By the 20th day, the meningeal signs had disappeared completely.

The above are only a few of the cases treated. Besides these, 29 cases of meningitis, including influenza, hemolytic staphylococcus and others have been treated with this method. The results were as shown in Fig. 6. The percentage of recovery in meningococcus was 100 per cent and that in pneumococcus meningitis was high.

The basis of therapy is to artificially increase the power of natural recovery of the body to the highest degree. Therefore, agents closest to the natural form should be used and those which may have a disturbing effect on the body should not be used. The injection of foreign substances into the spinal canal is especially dangerous and often results in untoward reactions. The use of various chemical agents and even antibiotics often results in fever, vomiting, convulsions and other side effects. An important factor in therapy is to prevent the occurrence of this type of effect as much as possible. In this sense it is believed that the injection of spinal fluid is significant. The basis for this is as follows:

1. It is the most physiological therapeutic method and there are absolutely no harmful effects.
2. Antibiotics need be used only in the early stage.
3. The occurrence of resistant strains is prevented.
4. There is no need to observe type as with blood, and the spinal fluid of any person can be used.
5. In cases where time is important and it is difficult to obtain the proper drugs, a certain effect can be obtained by the injection of spinal fluid alone.

Pathological Experiments in Animals

In order to examine the effect of spinal fluid alone, the following experiments were carried out:

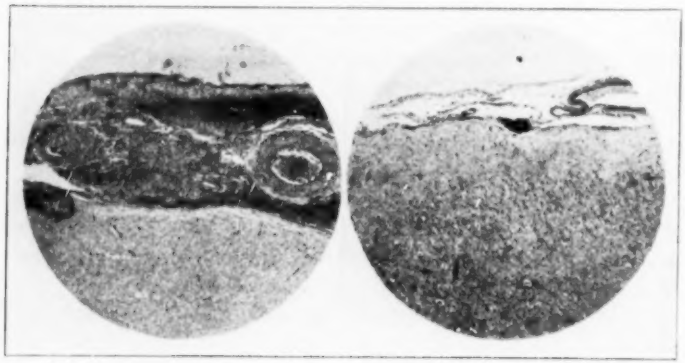
1. Dogs weighing approximately 5 kilograms were used in the experiments.

2. The bacteria used in the experiment were Pseudomonas pyocyanea which had been cultured on agar and incubated for 24 hours at 37° C.

3. Bacteria (1/20 gm.) were inoculated intrathecally by way of the suboccipital route and experimental purulent meningitis brought on.

4. Six dogs were divided into two groups of three animals each. In one group, the spinal fluid from normal dogs was injected. In the control group, physiological saline was injected.

5. The control animals died on the fifth day following inoculation so one of the treated animals was sacrificed at this time and histopathological examination of the brain carried out.



Control Treated

As shown in the photograms, the meninges of the control animal are thickened and hemorrhage can be seen. There is strong hyperemia and marked infiltration of cells. In contrast to this, there is only slight thickening of the meninges and slight cellular infiltration with no hemorrhage in the treated animal. Moreover, though all of the control group died, all the treated animals, except for the one which was sacrificed, survived and recovered completely.

DISCUSSION

It can thus be seen that the injection of normal spinal fluid is effective in purulent meningitis but explanation of the mechanism of action is difficult. It is believed that without doubt it is very complex. In order to try to clarify the biological response, at least

in part, the following experiments were carried out. An effort was made to find the effect of spinal fluid on the phagocytic action of the polymorphonuclear leucocytes.

Experiment 1. *Phagocytosis When Leucocytes and Bacteria are Treated Beforehand with Spinal Fluid.* Leucocytes and bacteria were treated beforehand under certain conditions with normal spinal fluid obtained from dogs and then combined in normal dog plasma and permitted to react. The degree of phagocytosis was then compared to a control in which physiological saline was used in place of spinal fluid.

Material. 1. Citrated Plasma and the Leucocyte Emulsion. To arterial blood drawn from dogs, 2 cc. of 3.8 per cent sodium citrate was added to make the total volume 10 mls. This was centrifuged and the citrated plasma separated.

The leucocytes were centrifuged and washed twice with sterile saline. To 5 ml. saline 0.5 ml. of the washed leucocytes was added and centrifuged once more. This was then emulsified in 2 ml. saline. (ca 1500/mm.^{3})

2. Bacterial Emulsion. Staphylococcus albus (Terashima strain) was grown on ordinary agar plant for 20 hours. A 0.5mg/ml. emulsion was made using this bacteria. This was washed and centrifuged twice. The turbidity of the emulsion was measured with a Nakamura electro-terbidometer and only the emulsions showing a turbidity of 21 per cent were used in the experiments.

3. Spinal fluid was drawn from normal dogs.

4. The leucocytes and bacteria were treated with the normal dog spinal fluid.

a. 1.0 ml. spinal fluid and 0.5 ml. leucocyte emulsion were mixed well and placed in a 37° C. water bath for 2 hours. This was then centrifuged and washed with saline twice. To this was added 0.5 ml. saline.

b. 1.0 ml. spinal fluid and 0.5 ml. bacterial emulsion were mixed well and placed in a 37° C. water bath for 2 hours. After centrifuging and washing twice, 1.5 ml. saline was added.

5. The above procedures were carried out as rapidly as possible (within 4 hours after drawing blood).

0.1 ml. plasma, 0.1 ml. leucocyte emulsion and 0.05 ml. bacterial emulsion were placed in a small test tube and mixed well. This was then placed in a water bath at a constant temperature of 37° C. and left for 15 minutes.

6. Smears were made in the usual manner. The slides were stained with Giemsa or Hosokawa's stain after fixing in methanol. Leucocytes were counted in groups of 200 and the number of leucocytes showing phagocytosis and the bacteria contained in each were determined.

Fig. 7

	Leucocytes and Bacteria Treated Beforehand with Saline		Leucocytes and Bacteria Treated Beforehand with Spinal Fluid		Ratio of Phagocytosis
	No. of Leucocytes showing Phagocytosis	No. of Bacteria engulfed (A)	No. of Leucocytes showing Phagocytosis	No. of Bacteria engulfed (B)	B/A
1	55	393	74	984	2.5
2	58	527	74	984	1.8
3	70	443	69	954	2.1
4	37	251	75	767	3.0
5	33	102	62	247	2.4
6	31	132	58	245	1.8

7. Results.

As can be seen in Fig. 7, the leucocytes which had been treated beforehand with spinal fluid show a greater phagocytosis and the number of bacteria engulfed is greater than in the control. The ratio is 1:2.

Fig 8

	Leucocytes and Bacteria Treated Beforehand with Saline		Leucocytes and Bacteria Treated Beforehand with Spinal Fluid		Ratio of Phagocytosis	Leucocytes and Bacteria Treated Beforehand with Fresh Serum		Ratio of Phagocytosis
	No. of Leucocytes showing Phagocytosis	No. of Bacteria engulfed (A)	No. of Leucocytes showing Phagocytosis	No. of Bacteria engulfed (B)	B/A	No. of Leucocytes showing Phagocytosis	No. of Bacteria engulfed (C)	C/B
1	26	102	60	544	5.3	60	752	1.3
2	25	46	41	55	1.2	35	66	1.2
3	19	27	23	49	1.8	40	53	1.0

Experiment 2. Phagocytosis when Leucocytes and Bacteria are Treated Beforehand with Fresh Serum. The same experiment as in Experiment 1 was performed with the exception of the addition of another group. A group in which the leucocytes and bacteria were treated beforehand with fresh serum was also examined and

the three groups compared. The procedures were identical with the preceding experiment. The bacterial emulsion and leucocytes were taken from the same sources.

Results:

Staphylococcus albus was used in groups 1 and 2 and Pseudomonas aerugynosa used in group 3. The phagocytosis seen with the serum treated group was almost identical with that seen in the spinal fluid treated group.

Experiment 3. Phagocytosis when Either the Leucocytes or Bacteria Alone are Treated Beforehand with Spinal Fluid. A comparative study was made of the phagocytosis resulting when the leucocytes were treated with the spinal fluid and the bacteria with saline and vice versa.

Fig 9

	Leucocytes Treated Beforehand with Saline. Bacteria Treated Beforehand with Spinal Fluid		Leucocytes Treated Beforehand with Spinal Fluid. Bacteria Treated Beforehand with Saline		Ratio of Phagocytosis
	No. of Leucocytes showing Phagocytosis	No. of Bacteria engulfed (D)	No. of Leucocytes showing Phagocytosis	No. of Bacteria engulfed (E)	D/E
1	38	111	25	60	1.7
2	32	93	22	75	1.2
3	36	110	23	55	2.0
4	28	71	25	53	1.3

It can be said from the results that the spinal fluid acts more strongly on the bacteria than on the leucocytes.

That the phagocytic action of the leucocytes is an important factor in the defense of the body against infection is an accepted fact ever since it was first reported by Metschnikoff. The fact that this phenomenon can be observed in vitro is utilized in many fields. Various methods may be used to examine the effect of spinal fluid on the phagocytic action of leucocytes. However, in order to study phagocytosis it is necessary to use plasma as a medium so one of the simplest methods would be to compare the degree of phagocytosis occurring when the material is treated beforehand with spinal fluid, serum or saline. It was found that prior treatment of the bacteria and leucocytes with spinal fluid caused a greater phagocytosis than

when treated with saline. In discussing the opsonin index of immune serum, a figure greater than 1:1.4-1:1.5 is considered significant. It can be said from the results of Experiments 1 and 2 that prior treatment of the bacteria and leucocytes with spinal fluid results in increased phagocytic action. From the results of Experiment 3 it is suggested that the spinal fluid acts more on the bacteria than on the leucocytes.

It is needless to say that phagocytosis is only one phase of the defense mechanism of the body, and it cannot be concluded from this alone that the spinal fluid therapy intensifies the defensive power of the individual. However, 2-4 hours after injection of spinal fluid, an increase in leucocytes is observed in the blood and the same phenomenon can be seen in the cerebrospinal fluid. Moreover, the phagocytic action of the leucocytes of the spinal fluid 5 hours after injection is increased two-fold. It can be seen from these facts that the intrathecal injection of spinal fluid causes a favorable change in the spinal canal and it can be said that this is a suitable form of stimulation therapy.

DRIED SPINAL FLUID

Normal spinal fluid is not difficult to obtain as it can be taken from the parents or other children but as it is necessary to continue the injections every day, there are cases where headache, nausea and in severe cases prostration when the spinal fluid is drawn from the same person day after day. This is of course only temporary and usually disappears within three or four days and there is no danger; however, it would be very convenient if unwanted spinal fluid, e.g. spinal fluid removed in hydrocephalus, could be stored and used when needed. Fortunately a large quantity of spinal fluid is removed each day in the treatment of poliomyelitis in the pediatric clinic. The spinal fluid of poliomyelitis patients, in which at least six months have elapsed since onset, is no different from that of normal. It is clear, the globulin reaction is negative, the sugar is normal and the cellular content is less than 3 per mm.[3]

This spinal fluid from poliomyelitis patients, showing no changes physicochemically or cytologically was dried after quantitative analysis of its various components. The dryings were by freezing and under reduced pressure. The vacuum dryer was developed in the department and the Elser freezing method was used to remove the water vapor. 10.0 mls. of spinal fluid was placed in a

12 cc. round drying ampule under sterile conditions and frozen in a solution of acetone to which dry ice had been added in order to lower the temperature to —60 to 70° C. It was then vaporized under reduced pressure in a vacuum drier using a "Cencohyvac" pump (pressure 10^{-3} mm. Hg.) and a powder was obtained. The ampule was then sealed and the dried spinal fluid stored in the dark at room temperature. The contents were examined once every month for one year. The following findings were observed: There is no change in the inorganic substances after one year. Protein content is also unchanged. It is believed that there was no change in the protein because of the method of drying used in the experiment. That is, the spinal fluid was first frozen and then dried under reduced pressure so there was no concentration of the material. The question of the relationship between protein and loss of water however is a problem left for the future. The substances most apt to be altered are the reducing agents and vitamin C. Both were somewhat decreased after 9 months, the former 5.7 per cent and the latter 6.4 per cent. Vitamin B_1 is unchanged. Cholinesterase had not lost its power to break down acetylcholine after 6 months. As for the cellular content there is room for study in regards to methods of preserving the cells morphologically and the staining solutions but as stated before the number of cells is so small that their value clinically can be disregarded. The dried spinal fluid was dissolved in sterile distilled water and tests of the effect on the phagocytosis of leucocytes carried out. The results were identical with those obtained using fresh spinal fluid. Dried spinal fluid was then tried in the treatment of purulent meningitis and the results were satisfactory.

It is believed from these results that dried spinal fluid can be stored for at least 6 months and that therapeutically there is little difference compared to fresh material.

CARDIAC AFFECTIONS IN POLIOMYELITIS. (Ugeskrift for Laeger, Copenhagen, 115:886, June 4, 1953). In the opinion of Georg and his associates a specific myocarditis may perhaps occur in some cases of poliomyelitis, but the majority of the histological and electrocardiographic changes described in this disease can undoubtedly be explained as results of anoxia and disturbances in the pulmonary circulation in patients with respiratory difficulty.—*Journal A.M.A.*

CLINICAL REVIEW

In order to encourage the writing of clinical articles by recent graduates or senior medical students, the ARCHIVES *will publish monthly at least one such paper from the classes of Doctor Reuel A. Benson, New York Medical College, New York, and Doctor Philip Moen Stimson, Cornell Medical School, New York. Other interested medical schools are cordially invited to submit student papers for consideration.*

THE MANAGEMENT OF INFANTILE ECZEMA*

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Infantile eczema is a synonym for atopic dermatitis in infants. "Atopic" denotes an allergic hypersensitivity characterized by a strong hereditary predisposition as shown by the eczema-asthma-hayfever complex. The diagnosis of atopic dermatitis in an individual should be substantiated by the following[1]:

1. The presence of a suggestive family history.
2. The presence of antibodies as demonstrated by the Prausnitz-Küstner transfer test.
3. Eosinophilia.
4. Response to scratch or intracutaneous tests by flare or wheal.

Of the above mentioned criteria family history and skin testing are the methods most commonly used. Passive transfer tests are difficult and time-consuming, and are usually used only in cases where the eruption is so generalized that ordinary skin testing is impossible. The presence of eosinophilia is so nonspecific that its existence alone would not be suggestive of atopy.

The presence of a positive family history is of significance in attempting to establish the presence of atopy. Hill[2] reports a positive family history of eczema, asthma or hayfever in 37 per cent of 184 cases under the age of twelve years. Six per cent of cases of a similar type have a normal family history. Kern[3] reports that in cases of established allergy, 35 per cent of the cases had one parent involved, while 65 per cent had both parents involved. These examples would seem to indicate that a positive family history is usually present and should be carefully looked into during routine history taking.

The status of skin testing in infantile atopy is not as definite

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as that of positive family history. This procedure is abused by many practitioners who interpret a positive reaction as conclusive evidence that removal of the offending antigen used in the test will solve the patient's problem. It would be advantageous if the problem were so simple, but there are too many factors influencing the test mechanism.

The mechanism of skin tests depends upon the pharmacological effect of histamine upon the blood vessels of the skin. The skin test dose of antigen simulates the conditions in the atopic child in which offending antigens are absorbed from the intestine, carried to the blood vessels of the skin, where they produce their effect. There are, in certain children, however, discrepancies in this chain of events which limits the value of the test. One important discrepancy lies in fact that some skins are anergic, i.e., will not react to an antigen for which a known sensitivity exists. This would result in a false-negative test. Another problem lies in the fact that many foods, which give positive skin tests, do not cause systemic reactions when administered in the usual manner in large amounts. This may be explained on the basis of partial absorption of proteins. In these infants the unsplit proteins are only slightly absorbed from the gut under ordinary circumstances, thus never reaching the shock organ in sufficient quantity to produce a reaction. This common occurrence produces a false-positive reaction.[4] These, as well as other more complex problems, prompt some observers[5] to state that skin tests and elimination diets are worthless. They feel that the offending food must be absorbed in an undigested allergenic form to cause a reaction. They say that this occurs with eggs and other highly allergenic foods, but not with the majority of offenders. To substantiate their claims, they mention a series of 124 cases in which hospitalization alone, without any other therapy, resulted in marked improvement of 50 per cent of the patients. This is about the same percentage obtained with the soybean type of diet and other regularly employed measures. This group suggests the gradual addition of suspected foods to the diet, as a valid test of suspected allergens. This method is somewhat unsatisfactory because it is too time-consuming and may severely "light-up" a susceptible child.

In spite of the difficulties involved, Hill[6] feels that skin testing is worthwhile. He feels, as do Sulzberger[7] and Cooke,[8] that a positive skin test means that a person may be atopic, but not

necessarily that the allergen in question is etiologic in the production of the dermatitis. The presence of even a trace of foreign protein in the test menstrum may cause a false-positive reaction. It must also be remembered that an atopic person may develop a positive test before the signs and symptoms of dermatitis begin, and that the test may remain positive after the person has been desensitized. Cooke feels that a positive patch test, especially in the absence of symptoms, is an omen of things to come, and may foreshadow the development of a more serious condition, viz., asthma, in later life.

Since the dermatologic approach to the problem of case management is fifty per cent of the therapeutic regimen, a brief discussion of the pathogenesis of the eczematoid type of reaction is in order.[9]

The process starts as an erythema, the shock organ consisting of the superficial blood vessels of the skin, viz., small capillaries and arterioles of the upper cutis. Histologically most changes occur in the epidermis, but the vessels of the corium are also involved. As the allergenic agent exerts its effect, the capillaries enlarge and fill with blood, resulting in the clinical condition of erythema. A defense mechanism, consisting of an inflammatory exudate of lymphs and histiocytes, surrounds the vessels. This is followed by an outpouring of serum which is usually enough to invade the epidermis, resulting in edema. This is the interstitial type of edema in which the staining properties of the skin are maintained. As this process continues, the prickle cells rupture, the staining properties are altered (light staining), and the stage of spongiosis results. When the cellular rupture becomes generalized, vesicle formation results. The increased serum content increases the nourishment and acanthosis results.

Clinically, the process may be described as passing from erythema, through papules, vesicles to the full blown case. From the vesicle stage the condition may proceed along three main directions: One, the vesicles may remain open after rupturing, resulting in the so-called weeping eczema; two, the vesicles may then dry up and scaley eczema is found; three, if the vesicles become infected, which is usually the case in infants, pustules followed by crusts are seen.

It is only fitting to mention at this point that a sharp separation between classic atopic dermatitis and contact dermatitis is less

favored today than formerly. Since the pathology in both conditions is produced by an irritation of blood vessels, the only essential difference is one of speed and degree of involvement.

The successful management of a case of infantile eczema requires a constant and vigorous pursuit of a more or less standardized regimen. Among the authors I have read, viz., Hill,[10] Wolpe,[11] Glaser,[12] there seems to be general agreement as to dermatologic therapy, dietary routine, etc. The chief disagreement lies in the interpretation and value of skin tests. Aside from the division of case management into general measures, including dietary and dermatologic measures, a modification of Glaser's routine provides a most complete, yet clinically workable, approach to the problem.

Glaser states, and rightly so, that there is no single completely satisfactory rubric to follow. One must adopt an attitude of conservative optimism; do the best that one can; since the disease is self-limited, it will probably pass after puberty. The physician must be wary of two facts. First, that it is impossible to tell who will grow out of the disease, and thus pass into puberty with a bad skin, with its concomitant adverse psychological effects. Secondly, the presence of atopic dermatitis indicates that we are dealing with an allergic child, and that the skin condition is a part or phase of cyclic chronic disease. The true object of treatment is to alleviate the present existing condition and to prevent the development of a worse allergy in the future, viz., asthma, by finding an adequate way of life for the patient.

A satisfactory routine should include the following:

1. *Prophylactic Measures.* These include any measure which may prevent the development of the condition in an infant. This would consist of measures to prevent development of congenital allergy by watching the diet of the mother during gestation.[13] The mother should not be allowed to eat highly allergenic foods, e.g., eggs and fish. This should also include offending drugs which may act as haptenes, such as, quinine, phenolphthalein and sulfanilamide. In the neonatal period, relief formulas of denatured milk may be slowly introduced, and thus reduce trouble at weaning. During later infancy, it should be remembered that the intestine will absorb split and unsplit protein indiscriminately. The relatively low efficiency of the infant digestive system permits a high percentage of allergenic protein to be absorbed. Cow's milk can provide 40 Gms. of protein for absorption, while mother's milk

provides only 15 Gms. The use of the latter should be encouraged on this basis. By the same token, complex foods, such as prepared cereals, etc., should not be started before the absorption becomes more discriminating, at least not before four to four and one half months. The fad among mothers of starting youngsters as early as possible on solids is responsible for many cases of dermatitis. During periods of infection, especially diarrhea and upper respiratory infections, no new foods should be added.

2. *Environmental Control.* This includes such measures as dust-free rooms and bedding. The avoidance of wool clothing, both for its possible allergenic properties and its irritating mechanical effect on the skin, is a good practice. Warm blankets consisting of two layers of cotton with fiberglas between may be purchased.

Under environmental control, hospitalization should be mentioned. Hospitalization is often advisable when the infant requires expert care. It also provides an allergenic-free environment when special rooms are used. The rest afforded the mother is also a help. In the hospital the infant may be seen by a physician as required; diets and restraints may also be expertly used. These advantages are somewhat offset by the complications of hospitalization. In the pre-antibiotic days, inevitable infection brought with it a rather high mortality. Schwartzmann[14] states that even with antibiotics the morbidity rate is higher than in those treated at home. In Epstein's[15] series there were two chief kinds of complications: One, skin infections, such as impetigo and other pyodermas, usually present, however, on admission. Two, respiratory and gastrointestinal disorders, the former pneumonia and the latter, diarrhea. He feels that their allergic nature makes them more prone to bacterial invasion that nonallergic infants. Many of the above mentioned symptoms are on the basis of allergy alone. As for fatal cases, he feels that antibiotics have reduced them to minute numbers. There are rare cases of sudden death reported. These cases are due to adrenal cortical failure of unsure etiology. Some of the theories include, systemic failure, i.e., Waterhouse-Friderichsen syndrome, anaphylactic shock, and toxic effects of absorbed phenols from coal tar ointment. For this reason it is a good precaution not to use coal tar on more than one extremity at a time; never on a raw surface. These cases will respond well to ACTH and cortisone.[16]

3. *Local Therapy.*[17] Under this heading is included those measures used to treat the skin, viz., solutions and ointments. This phase in the management of eczema is considered by many to be the most important of all, and to be the most abused and least understood by physicians. The chief difficulty lies in the fact that the physician fails to recognize the stage of the disease with which he is dealing, and thus prescribes the right drug at the wrong time. This, plus the failure to pursue a given course of therapy for an adequate period of time, is a common source of failure.

For practical clinical purposes the skin condition may be divided into three stages: The first stage is the edematous phase, in which the cells and their interstices are "water logged." The purpose here is to drain the tissues of their excess water by hypertonic wet dressings. Examples are potassium permanganate soaks, Burow's solution, boric acid, 2 per cent silver nitrate, ⅛-¼ per cent. As the second stage is reached, the medication is changed. Histologically there is no clear separation from stage one; however, there is a clinical difference. The difference lies in the cessation of "oozing," and the subsidence of erythema and itching. The rational lies in aiding nature in removing inflammation and edema. Two types of medicaments may be used. Pastes and tars are one type. These should be used sparingly and in conjunction with layers of gauze to absorb the run off. Ointments should never be used, since they stop drainage entirely. Some prefer "shake lotions," which are glycerine and alcoholic solutions of talc and zinc oxide. Examples of pastes are: Lassar's paste, U.S.P., and mentholated coal tars, 2-6 per cent. One should be cautious of infant sensitivity to the lanolin and cholesterol bases used in pastes. The third stage is characterized by lichenified, indurated plaques, seen particularly over the anticubital and popliteal areas, with or without the presence of infection. The object of treatment is to return the acanthomatous and hyperkeratotic skin to normal. Keratolytics and local skin stimulants are to be used. Some dermatologists believe that these agents are effective because the skin hyperemia produced summons an appropriate immunologic response of the skin. Example prescriptions are: 2-6 per cent ichthammol in Lassar's paste, pine-tar 25-50 per cent in a zinc oxide base, solution of coal tar, 5-10 per cent,

"Naftalan," (Donner) 6-10 per cent in Lassar's paste. The latter is particularly good. In using tars it is well to remember the possible effects of absorbed phenolic compounds, and it is suggested that they be used sparingly. They should be removed every few days by a suitable solvent, and another remedy used in the interim until they are reapplied. Patients with coal tar applied should not be exposed to the sun.

Antipruritics may be used at any stage, and are particularly valuable during the first and second stages. Phenol ¼ per cent may be added to solutions, so also may menthol, .1 per cent; benzocaine, 1-5 per cent is excellent but sensitization is frequent. Superficial x-ray therapy is helpful, but may not be used in the wet stages. Topical pyribenzamine, 2 per cent, is of questionable value.

The use of soap and water should be mentioned here. Ordinary soap and water should not be used, because the free alkali is quite irritating. Sulfonated soaps may be used, especially to remove old ointments which become irritating. Oils, such as olive oil and bland almond oil, should not be used for the same reason as ordinary soaps.

The restriction of motion, by means of ties in infants, and bandages in older children, is endorsed. This prevents scratching which not only delays healing, but favors infection.

4. *Systemic Medication.* The systemic routine[18] providing the best results for the relief of itching is the administration of pyribenzamine with phenobarbital. Demerol, ¼ of a 50 mg. tablet may also be used. Beware of the danger of addiction!

The following alterations in immunization procedures should be used: Give diphtheria, pertussis and tetanus but omit vaccination for smallpox. Never vaccinate until skin is clear; failure to observe this may result in a generalized vaccinia, or multiple vaccinations. Normal children in the household, if vaccinated, may give same to an eczematous child. By the same token, herpes should be avoided, since its spread may result in Kaposi's varicelliform eruption.

5. *Dietary Measures.* Most authors agree that milk substitute diets are essential or at least helpful in treating infantile eczema. The role of milk sensitivity is generally conceded to be important. In one series, Hill notes that most cases of eczema begin before the age of six months, and that the diet at this time consists mainly

of milk, orange juice, and synthetic vitamin D compounds. He also notes that eczematous children have a specific skin sensitivity to lactalbumin, and that non-eczematous children do not, as determined by intracutaneous tests. He finds that withdrawing milk in sensitive cases results in alleviation of symptoms in most instances. In addition to the sensitivity approach to the dermatitis problem, some recent work by Hansen[19] indicates that a deficiency problem may also be present. Hansen found that infants on a low essential fatty acid diet frequently incur respiratory infections and dermatitis. Both of these conditions may be relieved by the administration of essential fatty acids. He further noted that the serum iodine number of fats in eczematous infants is less than in normal infants, and that after administration of the fatty acids, the iodine number rose and the symptoms were alleviated. In his series of 171 cases, he found fatty acids to be a valuable adjunct to routine eczema treatment, and that 50 per cent of previously non-responsive cases improved markedly when essential fatty acids were given. The mechanism of action of these acids is unknown. No relation to an allergic mechanism was demonstrated.

There are those authors, however, who claim that the dietary approach is of minor importance. As mentioned previously, Osbourne[20] et al. state that diet is of importance in only 15 to 20 per cent of infants under the age of one year. They say that 50 per cent are markedly improved when hospitalized, in the ordinary children's ward, and placed on normal diets. He says that this is the same percentage of cures as obtained on milk substitute diets. He also feels that unsaturated fatty acids are of no value. Osbourne states further that eczematous response to ingested foods is the exception and not the rule. He bases this on the following observation: he has noted that hypersensitive children show symptoms of intestinal disturbance when ingesting a particular allergen. The typical reaction to this is urticaria. He feels that the eczema is secondary to the urticaria. Hill[21], on the other hand, has also pointed out certain foods, viz., egg white, fish, nuts, give rise to rapid explosive urticarial reactions, but not to eczema. Eczema is a slow cumulative affair, and never appears before the age of three months. These violent sensitizations acquired in utero, make subsequent sensitizations more easily acquired. By the time the eczema-

tous sensitizations are present, the original reactions may have lost their etiological significance, but they have paved the way for the atopic eruption.

In spite of the evidence and theory, pro and con, the use of milk substitutes is apparently widely accepted and used. There are probably as many routines for their use as there are hospitals. The essential pattern seems to be one of a diet of soybean substitute for a number of weeks, accompanied by suitable vitamins, with the gradual addition of foods of the regular diet, omitting the known offenders. The effects on the nutritional status of an infant placed on this type of diet for long periods of time have been studied by Wolpe.[22] He finds that those on denatured milk gained weight three and one-half times faster than those on soybean substitutes but those on substitute diets, etc., recovered twice as fast. After a year, the weight of both groups was the same. This would tend to influence one in favor of milk substi'utes.

6. *Finding and Eliminating the Causative Allergen.* This is probably the most difficult phase to carry out properly in the management of the allergic infant. The difficulties involved have already been discussed in the introduction. Hill feels that skin testing in spite of its difficulties has a place in the management of the eczematous infant. He feels that scratch tests are the best in infants, because there is less danger of a general reaction, and the amount of equipment required is less. Doubtful reactions should be followed by intracutaneous tests. The number of allergens that can be tested for are legion, but concentrating on the most common offenders as a guide to therapy is helpful.

Elimination diets are the best means of proving the allergenic nature of a suspected food in a particular individual. If a given food will cause a reaction, which will regress after a suitable period of withdrawal, there can be no disputing the wisdom of eliminating it from the diet of an infant. This method is too tedious for many cases, but by combining skin test results with elimination diets a reasonable conclusion as to etiology should be reached.

One should also remember that as the infant grows older the intestinal tract becomes more selectively absorptive, and that many of the foods offensive in childhood may be eaten again with inpunity. This is encouraging to the parents of severely allergic children who must follow strict diets.

In concluding this paper it should be said that the problems encountered in the understanding and management of infantile eczema are numerous and that there is no single or simple panacea for those afflicted. Although there is much disagreement among authorities, especially on the question of pathogenesis and value of skin tests, a practical approach to the problem of management, along the lines of the six points outlined above, should yield fairly good results.

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POLIOMYELITIS EPIDEMIC IN COPENHAGEN IN 1950. (Ugeskrift for Laeger, Copenhagen, 115:879, June 4, 1953). From late June 1950 to the end of the year, 110 cases of paralytic and 636 cases of nonparalytic poliomyelitis were treated in Blegdam Hospital. Children predominated, and there was a slight preponderance of males in the nonparalytic cases. The frequency of paralysis, in 15% of the entire group, the degree of severity, and the mortality increased with increasing age. Pregnancy seemed to increase morbidity and frequency of paralysis. There were also 136 cases of probable poliomyelitis, and 19 cases of polyradiculitis are considered because of their occurrence during the epidemic period. The epidemic curve reached its peak in September. The epidemic curve for polyradiculitis corresponded to that for poliomyelitis, but the age average was higher than that in poliomyelitis.—*Journal A.M.A.*

PEDIATRICS AT THE TURN OF THE CENTURY

From time to time the Archives, which was the first Children's Journal in the English language, will reprint contributions by the pioneers of the specialty over fifty years ago. It is believed that our readers will be interested in reviewing such early pediatric thought.

ACUTE CIRCUMSCRIBED EDEMA*

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New York.

SYNONYMS. Acute idiopathic edema, angio-neurotic edema, periodic swelling, urticaria tuberosa, giant swelling, acute non-inflammatory edema, Australian blight, Quincke's disease, giant urticaria, angio-neurotic erythema, hydrops hypostrophos.

In view of the facts adduced later it seems as though angio-neurotic and other terms connoting etiology should be abandoned in favor of Quincke's original name, Acute Circumscribed Edema.

DEFINITION. A disease characterized anatomically by circumscribed swellings varying in extent from the size of a papule to the involvement of a whole limb, appearing in the skin and mucous membranes or deeper connective tissues, and characterized clinically by their sudden appearance and disappearance, and the frequent association of gastrointestinal symptoms.

HISTORY. Since 1827 probable cases have been reported. It was described by Milton, in 1872, as giant urticaria. Arntz, in 1874, was the first to attribute a rôle to the neurotic element. It is to Quincke and his pupil Dinkelacker that we owe the establishment of acute circumscribed edema as a separate entity. Quincke's original article appeared in 1882. In 1885 Strübing gave it the name angio-neurotic edema. Since Quincke's original article it has engaged the attention of many observers on both sides of the Atlantic. On this side Osler has given us the best description, and Kohn, whose article appeared in 1901, has given the most complete bibliography up to that time.

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From the Bellevue Hospital Out-patient Department, Children's Service, First Medical Division.
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ETIOLOGY.—*Age.* It is most common in early adult life, the average age being twenty-seven years. It is rare after sixty. It is less frequently seen in children and but rarely in infants. Dinkelacker reports a case, male, one year, whose father was also subject to the disturbance. Crozer Griffith relates 1 case at two and one-half months, and another at five and one-half years. Ogden cites 2 cases, 1 a male of three months, the other a male of two and one-half months. Our own case was one year old. Falcone describes a case at seven years; the grandfather was also subject to the affection. Widowitz, 1 case, a female of seven years; another a male of eight years; a third, a male of six years. Johnston, 1 case, a female of five years.

Frequency. Hyde gives the frequency in America as 0.038 at all ages, while among about 1,200 consecutive cases of all kinds in our Children's Clinic we have met with but one instance of it.

Heredity. Heredity is well marked in some of the cases. Osler has traced acute circumscribed edema through five generations, twenty individuals being affected. Rolleston has described a persistent hereditary edema which is probably allied to acute circumscribed edema. Milroy has also described an hereditary edema. He traced it through six generations, numbering ninety-seven individuals, of whom twenty-two were affected. Osler considered one of Milroy's cases, as communicated to him, probably an angioneurotic edema.

Individual. There seems to be no connection either in children or adults with the physical condition of the patients affected. At all ages the patients may be either in excellent physical condition or emaciated and anemic. It is very common to find the patient neurotic, hysterical or neurasthenic. Menstruation, the climacteric, or even pregnancy may be an exciting factor.

Occupation. Occupation has no influence *per se*. Those subject to mental and bodily fatigue are more prone to attacks.

Season. It is more common in cold weather and in those parts of the body most exposed to the cold.

Sex. Males are affected twice as often as females.

Exposure. In Starr's experiment the edema was caused by cold water. The measurement around the knuckles before immersion was 195 mm.; after immersion 204 mm. There was a difference in the surface temperature of .8 of a degree. Exposure to the cold

air of winter may also cause the edema. Rarely, plunging the hands in hot water may excite the condition.

Trauma. Slight traumatism in those disposed is often followed by edema. Those parts of the body that have received injury or have been the seat of protracted pain are especially liable. Sometimes even a scratch is a factor in determining the onset.

Secondary. Alcoholism has a direct relation to acute circumscribed edema.

It also occurs in the course of Basedow's disease, hysteria and neurasthenia.

Psychical. Fright, grief, anxiety, and mental weariness have each been cited as the cause of an attack.

Food. This sometimes bears a relationship to the onset of the edema, although it is singularly slight as compared to its importance in urticaria. In children it plays a more important role than in adults.

Idiopathic. In some cases no cause can be found for the edema.

Clinical Varieties. The following two methods of grouping the clinical varieties are useful:

I. On an anatomical basis we can divide the clinical varieties into: (*a*) Those cases where the skin and deeper underlying tissues are alone involved. (*b*) Where the skin and some one or more of the viscera or joints are involved. The visceral lesions may occur in the alimentary canal, the respiratory system, or the kidneys. Sometimes the nervous system may be implicated.

II. Etiological factors determine a differentiation into clinical varieties. (*a*) In this group might be included the cases that originate in a toxic, autotoxic or infectious manner, come on acutely, run an acute course, like an intoxication or an infection, and have no tendency to relapse except so far as provoked by the same toxic insult. This group is allied to urticaria and purpura and often shows traces of these affections. (*b*) Under this heading might be included the cases where a direct or indirect heredity predisposes, where neurotic features stand out prominently in the disease picture, and where the attacks return independently of outside conditions with fatalistic regularity and definiteness.

PATHOGENESIS. Is it a symptom complex or a *morbus sui generis?* When occurring with Graves' disease, migraine, neuralgia, tabes, and organic cord diseases it must be looked on as

due to the same cause as the original disease. In some instances it might be considered as a morbid entity. In reviewing the literature on the subject one is struck by the fact that all the theories may be grouped under three heads.

(1) That the edema is due to an infiltration depending on blood pressure.

(2) That it is due to the secretory activity of the endothelium lining the blood vessels.

(3) That it is due to the nervous influences on the blood vessels.

In the cases that have been examined the blood pressure has varied but little from the normal, and as nothing is known of local changes in pressure, the first theory can be considered as highly improbable. It is probable that both the second and third enter into the true explanation. The simplest of all morbid processes is the disturbance of the circulation and congestive hyperemia, and the edema accompanying it. This is the beginning of all inflammation. Török has found that the albumin content of the edematous fluid in urticaria is higher than that of the simple transudate, from which it follows that the former is not to be looked upon as a simple filtrate, but has a manner of origin similar to the inflammatory exudate.

Fleeting edema, therefore, could easily belong to the inflammations as we have recognized them in the pathology of the skin, in their pure form, without disturbances of nutrition, and due to an active irritation in the vessels. The fleeting edema can alternate with a longer lasting edema, according to whether the cause works only very weakly and transiently on the vessel walls or in a stronger manner and for a longer time. The finding of the injurious material which acts on the vessel walls in this manner would be very difficult of accomplishment with our present knowledge of the toxins of metabolism. Experimentally, peptone has been found to be a vessel-irritating substance.

This explanation would be in accord with Heidenhain's teaching of the formation of lymph, which is, that it is the result of the secretory activity of the vessel endothelium, independent of increase of pressure and nervous influence.

This condition has a family relation with many of the arthropathies as yet not well understood but known to be directly caused

through the agency of the nervous system. There must first of all be a nervous system readily susceptible to reflex irritations, and the source of the irritations may be very slight and obscure; in fact, such as would altogether escape observation in a person without neurotic or neuropathic tendencies. It is probable that although the irritants act on other parts of the nervous system, the effects are most manifest in the distribution of the sympathetic. The incidence of the disturbance is mainly on the vasomotor supply in different localities, causing widening of the blood vessels and increased permeability of their walls. There then follows an outflowing of serum into the tissues producing the condition known as edema. The hyperemia accompanying a certain number of these cases lends color to the view that the vasomotor nerves are concerned. Whether the initial seat of disturbance is in the periphery or central nervous system is still a matter of conjecture.

When trophic changes occur, they are more plausibly attributed to the changes brought about by the oft-recurring edema than to influences exerted through the nervous system as trophoneuroses.

MORBID ANATOMY. As the disease is rarely fatal, except in cases where the larynx or lungs are involved, chances for post-mortem study are rare. The swellings are caused by an exudation of serum from the blood vessels unaccompanied by either red blood cells or white blood cells. The skin, mucous membranes, subdermal connective tissue, periosteum, or internal organs may be the seat. Rarely, as in Ebstein's case, the edema may go on to a true inflammation.

In the swellings connected with bone it has been found at operation that all the tissues are normal except the periosteum. In stripping this from the bone it has seemed a little rougher than usual. Chiselling into the bone has shown that it was normal. Where the swelling has been located over the cheeks operation has shown edema of the mucous membrane lining the antrum of Highmore.

In a fatal case the necropsy showed that the mucous membrane of the larynx was very edematous, tense and pale. The sides of the laryngeal cavity came in contact a short distance below the superior aperture, and remained so to just below the level of the true vocal cords. There was a small amount of viscid mucus. Transverse sections showed that the edema affected not only the mucous membrane, but the deeper connective tissue and even

the substance of the muscles. The edematous fluid was serous. The tissue covering the true vocal cords was decidedly affected.

In a case in which the stomach tube was used to control intractable vomiting it brought up a good-sized piece of the stomach mucosa. Microscopical examination of this tissue showed simply a marked infiltration of all parts of the mucous membrane with edema. In the small intestine there have been found at operation moderate-sized extravasations of blood and edema. In Harrington's case there was a considerable amount of clear fluid among the intestines and filling the pelvis. The intestines themselves were engorged with blood, and so red that a mild peritonitis was at first suspected. There were no hemorrhagic areas in the intestinal walls, but at a point within a short distance of the ileocecal valve a cylindrical enlargement of the ileum, 2½ inches long, entirely surrounded the gut, increasing the bowel circumference to twice its normal size. The swelling was evidently in the bowel wall, elastic to the touch, and did not pit on pressure. The finger could be inserted in the lumen of the gut at each end of the swelling.

SYMPTOMS. *Prodromata.* Prodromata are rare. Before the appearance of the swellings there may be vague feelings of malaise, general disinclination to exertion, chills, and ill-defined gastrointestinal symptoms, such as anorexia.

The onset is usually sudden. It is characteristic of the acute circumscribed edema that the swellings suddenly appear and disappear. They are fully developed in from a few minutes to six or eight hours, and cause very little trouble except by their mere presence. There is stiffness and the parts feel as if on the stretch. There is no pain or throbbing. They are clearly circumscribed, dense, and elastic in consistency. The color varies; it may be dark red, a roseate hue, or pale, almost waxy or whitish yellow. They do not pit on pressure, or very slightly. There may be slight scalding or burning as the swelling shows itself, and after this there may be slight itchiness, especially with the red color. The surface temperature is sometimes raised, sometimes lowered. They last from a few minutes to a few hours commonly, more rarely a few days. After the disappearance there is a wooden feeling. The parts are heavy and numb. Rarely there may be left some thickening or slight scaling of the skin. They recur in a few days or not for years.

Skin. The sites of election are the loose subcutaneous tissues,

namely, the lips, eyelids and cheeks. The hairy scalp is the rarest. Regions also affected are the nose, mastoid region, parietal region and occipital region. The whole face, including the ears, may be swollen. The swelling of the eyelids may be so great as to close them. The eyes may feel as if they were being pushed out. Some of the cases of recurrent exophthalmos may belong here. A finger, a hand, a forearm, or the whole arm up to the shoulder may be swollen. A foot, a lower leg, or the whole leg up to the groin may be swollen. Swellings have occurred over the crest of the tibia, each side of the Achilles tendon, and over the trochanter. The whole neck may be thickened, accompanied by pain. One side of the chest, abdomen or back may be swollen. The genitals may be swollen as a whole or merely the prepuce. The breast may be involved.

Mucous Membranes. Any part of the mouth may be affected as the cheeks or the tongue. The gums may be softened and there may be salivation. The nose, the tonsils, the pharynx, the larynx, and the conjunctiva may be affected.

The *mucous bursa* over the olecranon has been reported as the site of edema.

Gastrointestinal. Gastrointestinal symptoms occur in 34 per cent of the cases. For the first few years the manifestations are limited to the skin, when gradually the abdominal symptoms become prominent.

Stomach. There may be epigastric uneasiness, made worse by food, tension, loss of appetite, profuse vomiting and great thirst. In the severe attacks the picture is that of a gastric crisis. The vomitus is liquid and may be green and 1 to 2 quarts at a time. Examination of the stomach contents shows free hydrochloric acid present, no lactic acid. Boas' bacilli and yeast spores have been reported.

The pain ordinarily begins in the epigastrium and spreads over the abdomen. It is generalized pain, and does not radiate. At first the painful attacks may show themselves once a month and disappear after a few hours and without further disturbance, but later in the disease nausea and vomiting supervene in each attack. The pain is probably due to interference with the functions of the stomach by the edematous deposit.

Intestines. Intestinal symptoms are almost always associated with the gastric. There may be constipation and sharp, colicky

pains. Later diarrhea with no relation to food, occurring and ceasing suddenly, supervenes. There may be meteorismus and tender abdomen. The pain, as in the stomach, is probably due to the interference with the functions of the intestine by the edematous deposit.

Larynx. The throat is affected in 21 per cent of the cases. The symptoms come on suddenly, the voice is usually hoarse and almost inaudible. There may be pain in the neck, and a feeling as if something were sticking in the throat. Difficulty in swallowing may accompany the laryngeal condition, or there may be difficulty in swallowing alone.

Examination of the larynx shows edema of varying degrees and either unilateral or bilateral. There is edema over the epiglottis, as a rule. There may be edema of the arytenoid-epiglottic folds on one or both sides. In a severe case there are three rounded masses, pale, jelly-like, tense, representing the mucous membrane covering the epiglottis and two artytenoids. False and true vocal cords are completely concealed. The edema may extend to the subglottic region. The vocal cords when seen to be involved are somewhat reddened. In 1 case the laryngeal edema occurred repeatedly with each menstruation. In some cases the laryngeal edema is quickly followed by involvement of the lungs.

Lungs. The patient is suddenly seized with shortness of breath, actual dyspnea, or sudden cough, and rattling in the throat. This is followed sometimes by expectoration, which may be frothy and thin, or slimy and red, tinged with blood. As much as 200 cc. has been expectorated during an attack.

Microscopical examination of the sputum shows blood cells, squamous and cylindrical epithelium.

Examination of the lungs shows sibilant and sonorous breathing, and diffuse moist râles. In fifteen minutes the râles have been known to disappear entirely, and the respirations to drop from 45 to 15.

The pulse is usually unaffected with the lung condition.

Schlesinger thinks many cases of bronchial asthma belong here.

Nervous System. The sleepiness, dizzines, headaches, usually frontal or occipital, and the irritability, before the attacks, may be attributed to meningeal swelling.

Genitourinary. There may be slight painful micturition. There

may be polyuria, oliguria, albuminuria or hemoglobinuria. There may be even suppression of urine for a few hours. Some cases have shown an increase in the earthy phosphates and the presence of indican. With slight traces of albumin there are sometimes a few hyaline casts. Very often the urine is negative.

Fever. There may be an entire absence of fever. When present the temperature varies between 99° and 102° F. In adults the temperature seldom goes above 100° F. In children the range is somewhat higher.

Bones. The periosteal swelling may attack the bones of the head, the trunk, or the extremities. The frontal bone, the ribs, the humerus, the radius, the ulna, the metacarpals, and the phalanges have all been reported affected.

The x-ray picture shows no abnormal shadow, a proof that the periosteal swelling is edema and not blood.

Joints. The swelling of the joints is commonly, but not always accompanied by pain. The elbow joint and the maxillary joint have been reported as involved.

Muscles and Tendons. The swelling may be in the substance of the muscle or in the tendon sheath. The tendon sheaths of the back of the hand and the soles of the feet have been reported.

Glands. Tumefaction of the parotid and submaxillary glands has been observed. Possibly intermittent parotid swelling may belong to this class.

COURSE. The disease may begin in early childhood and recur only at rare intervals during the first few years. As the patient grows older recurrences grow more frequent until attacks are suffered nearly every week. The earliest attacks are mild and are limited to the swelling of the skin in various regions, when gradually abdominal symptoms become prominent. They are characterized by sudden onset and disappearance. They come on in the course of a few minutes or hours, last one or several days, then quickly disappear.

In another class of cases the edema does not appear until about the twenty-first year.

COMPLICATIONS. The visceral lesions are to be taken as a form of manifestation of the disease rather than as complications, and have therefore been discussed under symptomatology.

The condition is associated with exhaustion, debility and anemia.

In children there may be associated intestinal indigestion.

In rare instances the edema of the mucous membranes may go on to superficial nutritional changes, especially in the mouth.

Its occurrence in rheumatism is rather a coincidence than of etiological significance.

SEQUELAE. There are no serious after effects of acute circumscribed edema. The parts, as a rule, return to normal. Rarely the skin remains thickened when the edema has been of long duration. In severe cases there may be slight scaling of the epidermis.

DIAGNOSIS. The diagnosis is, as a rule, not difficult. The following points should be borne in mind: The swellings are rapid in appearance, have more or less sharp limitations, a pale or normal color, more rarely somewhat reddened, accompanied by a discomfort which is merely a feeling of tension, or slight (rarely marked) itching. The swellings do not pit at all or only slightly. They are multiple and usually disappear after a few hours or days. There is likely to be a disappearance of one and a simultaneous appearance of another. The disposition to renewed attacks in varying or constant intervals is present. They have a preference for a place already attacked before. Associated with the skin swellings there are in many cases sudden appearance and disappearance of internal symptoms. The patient may have a nervous temperament.

There seems to be no doubt that it is nearly related to urticaria, certain cases of Raynaud's disease, purpura and erythromelalgia.

In hysteria there are two forms of edema, the white edema, or Sydenham's edema, and the blue edema, or Charcot's edema. It is associated with other hysterical symptoms. There may be paralyses, contractures, or anesthesia. It occurs in adults. It is usually unilateral and the face is free. The color of the skin changes and may be white, cyanotic or red. It can appear and disappear suddenly, but is, as a rule, of long duration. It is not multiple. In many cases the diagnosis is difficult.

In the edema with neurasthenia there is evidence of some of the multifarious manifestations of the neurasthenia. In idiopathic chronic neuropathic edema the hereditary element is strong, and it is confined to certain localities. In stabile edema there is a history of repeated erysipelas, the edema is persistent

and always in the same locality, and there are evidences of past inflammation. In erythema nodosum the lesions are usually small, they occur most frequently on the lower extremities and are sensitive to pressure. The color is usually dusky and a distinct induration accompanies the lesion. After the subsidence spots like the discoloration of old bruises are left. There are constitutional symptoms, such as elevation of temperature and pulse.

In urticaria the lesions are smaller, as a rule, though they may be as large. They are bright red, and though the centre may be anemic the border is red. Urticaria has itching as a constant symptom.

Australian blight is confined to the locality from which it takes its name. The edema of nephritis is not readily mistaken for acute circumscribed edema. In conjunction with the other symptoms of nephritis the edema is stabile, occurs more in the dependent parts, pits on pressure, and is relieved by rest and posture.

In edema neonatorum there is low temperature, coldness of the surface, and it is widespread, and pits on pressure, though with difficulty. It occurs in weakly or premature infants, usually before the third day of life. The child is apathetic and unable to nurse. The pulse and respiration are slow and weak. Death nearly always occurs.

In erythromelalgia one or more of the extremities, usually the feet, are subject to pain, flushing and local fever, made far worse if the parts hang down. It is chronic.

In making the diagnosis from gall stones, appendicitis, intussusception, or obstruction of the bowels, Osler's advice may well be quoted here. After relating 3 cases which were operated on, he says: "The practical lessons to be drawn from these 3 cases in which laparotomy was performed are first, that with children with colic the greatest care should be taken to get a full history, which may bring out the fact of previous attacks, either of the skin lesions, of arthritis, or of intestinal crises; and, secondly, to make the most careful inspection of the skin for angioneurotic edema, purpura, or erythema."

In edema of the larynx the secondary edema of tuberculosis or syphilis is to be thought of. Against these are the suddenness of onset, the lack of marked cough and of local pain.

According to Quincke, against erysipelas of the larynx are the

facts that, anatomically, there is not much else than edematous swelling, the good general condition and continuous apyrexia.

From cellulitis the diagnosis on the appearance of a single swelling is sometimes difficult. But here there is pain, temperature, permanence of the lesion, pitting on pressure, swelling of the lymph nodes, and sometimes a site of entrance of the infection can be determined. In the case related below when one arm was swollen up to the shoulder, it was mistaken for cellulitis, and incised in the palm. The incision, of course, revealed no pus. It healed kindly. Other cases are recorded where incision has revealed the true nature of the lesion.

Where the lungs are involved, giving either the picture of asthma or edema, the diagnosis can be made only by exclusion. In any of the visceral lesions where swelling of the skin is present the diagnosis is much simplified.

PROGNOSIS. In all forms of acute circumscribed edema, except where the larynx is involved, spontaneous recovery takes place. In laryngeal involvement death sometimes takes place, and the prognosis is therefore grave.

TREATMENT. In involvement of the respiratory tract any local disease should be corrected, which may have to do with the localization of the lesions in the air passages.

In edema of the fauces, pharynx or larynx, adrenalin and cocain should be used locally. In more severe cases scarification, intubation, or tracheotomy may even be indicated. Ice, locally, may add to the edema. There should be rest in bed and removal from anxiety.

All the systems of the body should be put in the best possible condition. Strychnin to the physiological effects may be tried.

Alimentary disturbances should be regulated with cascara and nux vomica, saline laxatives and sodium salicylate. As alteratives and tonics, arsenic and iron in large doses should be employed. Atropin has been administered with benefit. Drug treatment may be advantageously supplemented by massage. Hygienic conditions should be improved.

Bloodgood, of Johns Hopkins, has reported a case of angioneurotic erythema of both cheeks relieved by neurectomy of the infraorbital nerves. A second area on the left side of the abdomen was relieved by the division of the intercostal nerves.

The affection is obstinate and, as a rule, treatment to be effective must be prolonged.

REPORT OF CASE.

The patient, P. M., male, an infant one year old, was admitted to our Clinic in the Out-patient Department of Bellevue Hospital on May 16, 1904. The father was a native of England and had had some lung affection, for which he had been under treatment and had been discharged cured. The mother complained of headaches and dizziness and an examination of her urine showed a marked trace of albumin.

The child had been on the breast up to the present time, and for the first six months exclusively. Then a crust of bread and soup was added to his feedings. At nine months he was given oatmeal, mashed potatoes and plasmon, ½ teaspoonful once or twice a day. At eleven months he was allowed plain cow's milk.

Up to seven weeks ago the patient had been perfectly well. At this time he had an attack of measles that ran an uneventful course, according to the mother's statement, but two weeks later he had a convulsion that was attributed to cutting teeth, and this occurred again three weeks ago, or two weeks after the first.

The present illness was attributed to a meal of cabbage and potatoes given to the child by an officious friend the day before the onset. On May 9th, the day after the delectable meal, there appeared a red spot on the left leg, which the mother described as a "pimple with a red circle about it." The next morning, May 10th, at 4:30, the baby awoke screaming. The mother found the left leg swollen "as if it would burst," right up to the groin. This condition lasted one day.

On May 11th, in the morning, the left arm from the hand to the shoulder was swollen. This also lasted one day.

On this day, two days after the onset, the bowels began to be loose. The stools were five or six in number, green, and accompanied by a good deal of rumbling and wind. They were watery and contained curds. The bowels remained in this condition for four days, up to May 15th, the day before admission.

On May 12th, in the morning, the right arm from hand to shoulder was swollen. On this day the mother took the child to a public clinic, where a diagnosis of cellulitis was made and a deep

incision carried into the palm of the hand. The mother said that no pus was found and, indeed, the appearance of the wound showed no signs of suppuration.

On May 13th, in the morning, the whole of the right leg was swollen up to the groin. The little patient passed no urine all that day. The mother administered sweet spirits of nitre and some urine was passed the next day.

On the morning of the 14th two massive swellings appeared on the scalp, covering the parietals from front to back and separated by a deep depression along the sagittal suture.

On the 15th the swelling made its appearance on the occiput. This day the patient passed very little urine.

On the day of admission, May 16th, in the morning, massive swellings appeared on the left lower chest and abdomen, and another on the back. He had passed no urine from 6 A.M. to 3 P.M.

The baby has taken the breast well during the whole illness, and the mother has nursed him very frequently to quiet him. The mother says the baby has had no colic, but has been feverish and has perspired freely.

Status Presens. The child is well nourished, but of pale color. Weight, 20 pounds, 2 ounces. Length, 28 inches. Circumference of head, 18½ inches. Circumference of chest, 17 inches. Circumference of abdomen, 18½ inches. The right leg is swollen throughout its length, most marked below the knee and in the foot. The leg is held semi-flexed and the child evidences pain on passive motion. Active motion seems also to be painful. The circumference of the right leg is 1 inch larger than the left.

The tissues over the right elbow are swollen and tender. In the palm of the right hand is the wound of incision, healing by granulation. Over the small of the back is a massive oval-shaped swelling measuring 4x5 inches. There are small red spots varying in size from a pin head to a ten-cent piece, which fade on pressure, scattered over this swelling and the rest of the back. Over the whole left side of the abdomen and lower chest, and extending 1 inch to the right of the median line, is another swelling of the same kind. Over the right malar bone and outer angle of the right eye was a similar swelling which disappeared during the examination. A swelling of the same kind appeared over the right

parietal region. There is still another mass over the occipital region. The scrotum is diffusely swollen, but the testicles do not seem to be involved.

All of these swellings were hot to the touch and did not pit on pressure.

There were no ecchymoses.

The anterior fontanel is open ¾ of an inch, and there is a faint suggestion of craniotabes. The gums were not spongy, nor even congested. Tonsils were slightly enlarged and a few adenoids were present. The anterior and posterior cervical glands were palpable. There was slight beading of the ribs. Lungs and heart negative. The abdominal muscles were held too rigid to palpate the contents of the abdominal cavity satisfactorily.

Rectal temperature 102° F.

Breast and other food was stopped, and the child was put on barley water, oz. vi., q. 2 h. Calomel was administered.

On the 17th there was a swelling on the right side of the head.

On the 18th the patient was much better. The remains of the swelling on the back were still visible, and that of the leg much diminished. The tenderness was gone. A few small erythematous patches were present on the back and small copper-colored spots on the left arm. Over the pubes a little swelling still persists. The abdomen is palpable, and no liver or splenic enlargement can be made out. The child is urinating more freely and the rectal temperature is only 99.5° F. More calomel was ordered and mutton broth alternated with the barley water.

The child was seen again on May 20th and had steadily improved. No fresh swellings had appeared since the 18th, and the old ones were no longer visible. There were a few red spots over the pubes. Examination of the urine (the first sample obtainable) showed a little albumin. A little cow's milk was added to the feedings.

After this date the patient ceased to come to the Clinic, presumably because the condition had disappeared. An effort was made to trace the case, but as so commonly occurs, the address proved to be a false one.

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